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Smoke and mirrors: are adolescent cannabis users vulnerable to cognitive impairment?

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Concise statement: A growing body of evidence challenges the assertion that adolescence represents a period of vulnerability to neurocognitive harms of cannabis use. Innovative and cross-discipline methodologies are required to address limitations and work towards reliable public health messages.

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Reporting in *Addiction* (1) on data from the Environmental Risk Longitudinal Twin Study (E-Risk), Meier et al. found no evidence that adolescent cannabis use or dependence was associated with IQ decline between the ages of 12 and 18 years. Moreover, they found no difference in age 18 IQ between co-twins discordant for cannabis use and minimal differences in executive functioning, suggesting family background factors may explain lower neurocognitive performance often reported in cannabis users. The authors therefore conclude, "...relatively short-term cannabis use in adolescence does not appear to cause IQ decline or impair executive functions, even when cannabis use reaches the level of dependence."

As Meier et al. discuss, these findings are in line with a number of recent prospective cohort studies on cannabis use and neurocognitive performance, in which outcomes were assessed during adolescence or early adulthood (2-5). Of interest, Meier et al. draw a comparison between these studies and two other cohorts with follow-ups in older adulthood that instead did find evidence of neurocognitive decline in cannabis users (6, 7). Without longer follow-up, whether impairment will emerge in later life in the younger cannabis users is not clear. However, given the common assumption that cannabis use in *adolescence* is particularly detrimental to neurocognitive functioning, relative to delaying use until adulthood, the lack of impairment in young cannabis users is of interest.

Assertions that adolescence represents a period of vulnerability to neurocognitive harms of cannabis use are largely based on a previous, highly influential study by Meier and colleagues using the Dunedin cohort (6). Here they reported that adolescent- but not adult-onset cannabis users experienced IQ decline, but only in those who had persistent, heavy cannabis use or dependence during adulthood. Some (8-13), though certainly not all (14-17), smaller cross-sectional studies have also found evidence of lower performance in early- compared to late-onset or non-users, or of associations between age of onset and performance. There is however very little consistency across studies, particularly in terms of affected cognitive domains.

An important consideration, as highlighted by Meier et al. (1), is that only 1% of the E-Risk cohort used cannabis multiple times a day. Could this very heavy level of use cause neurocognitive decline in adolescence, which was not detected in the E-Risk cohort? In order to test this, Meier et al. point out that larger cohort studies will be needed, such as the recently initiated Adolescent Brain Cognitive Development study (n=10,000) (18). However, since very heavy use is rare in the general population, even large cohorts may not be adequately powered to test such effects.

One way to address this issue is to recruit according to pre-specified cannabis use levels, ensuring that heavy-users are over-sampled. Such a design, implemented longitudinally, could increase statistical power to assess neurocognitive trajectories associated with long-term heavy cannabis use in adolescence and beyond. Importantly, comparisons between early- and late-onset users are often substantially confounded by longer duration and heavier cannabis use (e.g. three times the quantity and twice as often (11)) in early-onset users. To better address the question of adolescent vulnerability, innovative methods of matching participants (e.g. propensity score matching) of different ages and ages of onset on key cannabis use variables and other factors, could reduce (though never completely eliminate) this potential confounding.

Placebo-controlled studies can also complement observational methods, allowing assessment of causal effects of cannabis exposure in different age groups. Indeed, we recently showed contrasting patterns of acute cannabis effects in adolescent and adult cannabis users (19). Specifically, adolescents experienced blunted intoxication and memory effects of cannabis, offering preliminary evidence that adolescents may be resilient to some acute effects of cannabis. As cannabis policy

changes, randomised controlled trials testing effects of repeated administration of medicinal cannabis products on neurocognitive functioning in certain populations may also become feasible.

In conclusion, this paper adds to a growing body of evidence challenging the assertion that adolescence is a period of vulnerability to putative neurocognitive harms of cannabis use. It is important that, while the evidence remains unclear, the risks to teenagers using cannabis, parents, and policy-makers alike are not over-stated. Further research using innovative and complementary methods will be key in advancing our understanding of age-related differences in vulnerability.

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